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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,541	06/21/2001	Thomas J. Brennan	R-17	5815

7590 12/18/2002

DeltaGen., Inc.
740 Bay Road
Redwood City, CA 94063

EXAMINER
PARAS JR, PETER

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/18/2002 12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,541	BRENNAN ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *1-7,9 and 11-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III, claims 8 and 10, in Paper No. 11 is acknowledged. The traversal is on the ground(s) that searching all the claims would not be an undue burden for the Examiner. In particular, Applicants submit that it would not have been undue to search the claims of Groups I-VI, since all of the claims in the groups are related. This is not found persuasive because it is maintained that each of the Inventions require a separate search status. In particular, it is maintained that the products of Groups I, II, III, and IV are different each from the other; they each have different chemical structures and can be used in materially different methods that require different technical considerations. For example, the DNA targeting construct of Group I can be used to disrupt a cerberus gene in a somatic cell *in vitro*, the cells of Group II can be used to produce a protein *in vitro*, the transgenic non-human animal of Group III can be used as a model of disease, and the unknown agents of Group VI can be used for modulating the function of a cerberus protein in a somatic cell *in vitro*. It is maintained that the products of Inventions I, II, III and VI are distinct due to their divergent subject matter (DNA targeting construct, transgenic non-human animal, unknown agent that can modulate the function of a cerberus protein) and are separately classified and searched.

It is maintained that the methods of Groups IV and V are distinct, comprising different methodologies and using different products. For example, the method of

Group V can be practiced in a somatic cell *in vitro*, while the method of Group IV is required to be practiced in a transgenic non-human animal. It is maintained that the methods of Groups IV and V are distinct as they are directed to different methods that require the use of different products that need different technical considerations (somatic cells *in vitro* and transgenic non-human animals) and are separately searched and classified.

It is maintained that the products of Groups I, II, III and VI are distinct from the methods of Groups IV and V; the products of Groups I, II, III, and VI can be used in methods, which require different reagents and technical considerations from the methods of Groups IV and V. For example, the DNA targeting construct of Group I may be used as a probe in a hybridization assay *in vitro* while the transgenic non-human animal of Group III may be used to produce antibodies to an antigen, while the method of Group V may be used to identify agents that modulate the expression of a ubiquitin-specific 16 protease. The method of Group V may be practiced with agents that have different chemical structures from the agent of Group VI. It is maintained that the products of Groups I, II, III and VI are distinct from and can be used in different methods (hybridization assays, generating antibodies) from the methods of Groups IV and V.

Therefore it is maintained that all the inventions are distinct each from the other for the reasons given above. The requirement is still deemed proper and is therefore made FINAL.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the

Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 1-7, 9, and 11-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a homozygous disruption in the nucleotide sequence set forth in SEQ ID NO: 1, wherein said mouse exhibits the following phenotypes as compared to a wild-type mouse: an increased response latency to lick or fan a hindpaw on the hot plate test, and a tendency to spend more time in the central region on the open field test. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a transgenic non-human animal comprising a disruption in a platelet-activating factor receptor gene and a method of producing a transgenic mouse.

The specification teaches the generation of transgenic mice by disruption of the nucleotide sequence set forth in SEQ ID NO: 1. See pages 6, lines 15-25, and the working examples on pages 51-53 of the specification. The specification teaches that the transgenic mice exhibit the following phenotypes as compared to a wild-type mouse: an increased response latency to lick or fan a hindpaw on the hot plate test, and a tendency to spend more time in the central region on the open field test, as a result of a homozygous disruption of the nucleotide sequence set forth in SEQ ID NO: 1. See pages 51-53 of the specification. While the specification has taught the generation of such a transgenic knockout mouse, the specification has not taught the generation of the other transgenic non-human animals comprising a disruption in a platelet-activating factor receptor (PAFR) gene encompassed by the claims. The working examples, guidance and relevant teachings provided by the instant specification are directed to the creation of the above transgenic mouse but do not support the creation of other transgenic non-human animals encompassed by the claims. See pages 51-53.

With regard to claim breadth, the standard under 112, first paragraph entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, in light of the

specification, the claimed invention is properly interpreted with regard to the disclosed phenotype of the exemplified transgenic mice comprising a disruption of the nucleotide sequence set forth in SEQ ID NO: 1. Such an interpretation is consistent with the specification despite that the claimed non-human mammals require only that they comprise a disrupted PAFR gene. This is because, with regard to the enablement requirement, one of skill in the art must be provided with both how to make and use the claimed invention. As such, the enabled scope of the claimed invention, in light of the teachings of the specification, is found to be the generation of transgenic mice comprising a homozygous disruption of the nucleotide sequence set forth in SEQ ID NO: 1 which exhibit the following phenotypes as compared to a wild-type mouse: an increased response latency to lick or fan a hindpaw on the hot plate test, and a tendency to spend more time in the central region on the open field test.

The following aspect of the rejection under 35 U.S.C. 112, first paragraph is directed to the use of embryonic stem cells to create transgenic knockout non-human animals:

Both the specification and the state of the art have taught that the transgenic knockout technology requires the use of embryonic stem cells that have been genetically manipulated to comprise a disruption in a nucleotide sequence of interest. The specification has not taught creation of a transgenic knockout non-human animal by methods that do not require embryonic stem cells. Presently, the transgenic knockout technology is limited to the mouse system. See below.

With regard to the claim breadth directed to transgenic non-human animals, the specification fails to teach the production of any transgenic non-human animal comprising a disruption in a PAFR gene other than a transgenic knockout comprising a disruption in the nucleotide sequence set forth in SEQ ID NO: 1. It is well known in the knockout art that the production of knockout animals other than mice is undeveloped. This is because ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species. See Moreadith et al. at page 214, Summary. Seamark (Reproductive Fertility and Development, 1994) supports this observation by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Likewise, Mullins et al. (Journal of Clinical Investigation, 1996) state that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page S38, column 1, first paragraph). As the claims are directed to a transgenic non-human animal, which must be generated by the introduction of a transgene into an ES cell or a method of producing a transgenic mouse by introducing a targeting construct into any cell, the state of the art supports that only mouse ES cells were available for use for production of transgenic mice. Also claim 8 as written does not require that the disruption is transmitted through the germline and can be interpreted to read on a mouse comprising a disruption of a PAFR gene in a single cell. Limiting claim 8 to a transgenic mouse whose genome comprises a homozygous disruption of the nucleotide sequence set forth in SEQ ID NO: 1 and claim 10 to an ES cell would be sufficient to

overcome this aspect of the rejection. Given the unpredictable state of the art it would have required undue experimentation for the skilled artisan to create transgenic knockout non-human animals of species other than the mouse or to use any cell for creating the same transgenic knockout animals.

Claim 8 encompasses a transgenic non-human animal that comprises a disruption in a PAFR gene that does not exhibit any particular phenotype. The state of the art at the time of filing was such that one of skill could not predict the phenotype of a knockout mouse (Moreadith et al., 1997, J. Mol. Med., Vol. 75, pages 208-216; see page 208, column 2, last full paragraph). Moens et al. (Development, Vol. 119, pages 485-499, 1993) disclose that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (see abstract). The specification has asserted that the nucleotide sequence set forth in SEQ ID NO: 1 encodes a PAFR. However, it would be difficult to predict any phenotype resulting from disruption of the sequence of SEQ ID NO: 1 in light of the above. The specification discloses that the phenotypes exhibited by knockout mice comprising a homozygous disruption in the nucleotide sequence set forth in SEQ ID NO: 1 are: an increased response latency to lick or fan a hindpaw on the hot plate test, and a tendency to spend more time in the central region on the open field test. See pages 51-53 of the specification. Claim 8, as written, does not include a phenotype that differs from the wild-type mouse. Moreover, the skilled artisan would know how to use a transgenic knockout non-human animal that lacks a phenotype, particularly because the instant specification has not provided uses

for such; the transgenic mice that have a phenotype of : an increased response latency to lick or fan a hindpaw on the hot plate test, and a tendency to spend more time in the central region on the open field test as compared to a wild-type mouse may be used for drug testing according to the instant specification. The specification overcomes the unpredictability in obtaining a phenotype associated with a disruption of the nucleotide sequence set forth in SEQ ID NO: 1; however, the claim is not commensurate in scope with the enabled phenotype disclosed in the specification. Inclusion of a phenotype associated with a disruption of the nucleotide sequence set forth in SEQ ID NO: 1 in a mouse in the claim would overcome this aspect of the rejection. As discussed above, claim 8 as written can be interpreted to read on a mouse comprising a disruption of a PAFR gene in a single cell, which is unlikely to result in a phenotype different from a wild-type mouse because PAFR protein is still produced. Given the unpredictable nature of a phenotype that results from disruption of a nucleotide sequence it would have required undue experimentation for the skilled artisan to use a transgenic non-human knockout animal that lacks a phenotype.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the production of transgenic non-human animals comprising a disruption in a PAFR gene, the lack of direction or guidance provided by the specification for the production of transgenic non-human animals comprising a disruption in a PAFR gene, the absence of working examples for the demonstration or correlation to the production of a transgenic knockout non-human animal that exhibits a phenotype other than the exemplified mouse, the unpredictable state of the art with

respect to a phenotype that results from disruption of a given nucleotide sequence, the undeveloped art pertaining to the establishment of true embryonic stem (ES) cells of animal species other than mouse, and the breadth of the claims drawn to all non-human animals, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.
Art Unit 1632

Pete Paras
Art Unit 1632